Network Effects of Brain Lesions Causing Central Poststroke Pain

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Objective: This study was undertaken to test whether lesions causing central poststroke pain (CPSP) are associated with a specific connectivity profile, whether these connections are associated with metabolic changes, and whether this network aligns with neuromodulation targets for pain.
Methods: Two independent lesion datasets were utilized: (1) subcortical lesions from published case reports and (2) thalamic lesions with metabolic imaging using 18F- fluorodeoxyglucose positron emission tomography–computed tomography. Functional connectivity between each lesion location and the rest of the brain was assessed using a normative connectome (n = 1,000), and connections specific to CPSP were identified. Metabolic changes specific to CPSP were also identified and related to differences in lesion connectivity. Therapeutic relevance of the network was explored by testing for alignment with existing brain stimulation data and by prospectively targeting the network with repetitive transcranial magnetic stimulation (rTMS) in 7 patients with CPSP.
Results: Lesion locations causing CPSP showed a specific pattern of brain connectivity that was consistent across two independent lesion datasets (spatial $r = 0.82$, $p < 0.0001$). Connectivity differences were correlated with postlesion metabolism ($r = -0.48$, $p < 0.001$). The topography of this lesion-based pain network aligned with variability in pain improvement across 12 prior neuromodulation targets and across 32 patients who received rTMS to primary motor cortex ($p < 0.05$). Prospectively targeting this network with rTMS improved CPSP in 6 of 7 patients.
Interpretation: Lesions causing pain are connected to a specific brain network that shows metabolic abnormalities and promise as a neuromodulation target.

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Central poststroke pain (CPSP) is a neuropathic pain syndrome caused by cerebrovascular lesions.[1] Many of these lesions are in the posterior thalamus, intersecting the ventral posterolateral nucleus (VPL) or its boundary with the anterior pulvinar nucleus.[2–5] However, lesions outside the posterior thalamus can also cause pain,[2,6–8] leaving localization unclear. Furthermore, focal lesions causing CPSP can have functional effects on remote but connected

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brain regions, further complicating attempts at localization.[2,9,10] Identifying the neuroanatomical substrate for CPSP, including potential network effects, is important for better understanding this complex syndrome, but may also be clinically important for guiding therapies such as transcranial magnetic stimulation (TMS), deep brain stimulation, or ablative neurosurgery.[9,11] These neuromodulation therapies have all been used in the treatment of CPSP and neuropathic pain in general, but the neuroanatomical target remains unclear. As such, a dozen different brain regions have been targeted using a largely trial-and-error approach, with primary motor cortex (M1) emerging as the most effective target for pain for unclear reasons.[9,11,12]

Lesion network mapping is a technique in which focal brain lesions causally associated with specific symptoms or disorders are mapped onto brain networks using a normative connectome.[13] This approach has provided insight into lesions associated with tremor, Parkinson disease, dystonia, depression, and many other conditions.[14–17] More importantly, networks identified using this approach align with the efficacy of neuromodulation treatment targets for these conditions.[14–18] Prior work from our group and others suggests that this lesion-based approach may be useful in mapping pain.[2,19] However, these prior studies lacked an independent validation cohort, well-matched control lesions, or functional imaging in lesion patients to test whether regions connected to pain lesions are actually abnormal in patients with CPSP. Finally, it remains unclear how lesions causing pain relate to the efficacy of neuromodulation treatment targets for pain, including our most effective target in M1.

In this study, we examined the brain network effects of lesions causing CPSP using lesion network mapping and alterations in metabolism using 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET). We tested the following hypotheses: (1) lesion locations associated with CPSP will show significant differences in functional connectivity compared to well-matched control lesions, (2) functional connectivity differences will be consistent across independent datasets, (3) functional connectivity differences will correlate with differences in poststroke metabolism, and (4) the brain network identified by these analyses will align with effective brain stimulation targets for neuropathic pain.

Materials and Methods

Lesion Datasets

Two independent lesion datasets were included in this study, both of which have been published previously.[10,19] These datasets were selected because they included lesions associated with CPSP, matched control lesions not associated with CPSP, and were readily available. This study was not meant to be a comprehensive analysis of all CPSP lesions in the literature.

Dataset 1: Lesions from the Literature

The first dataset consisted of 63 subcortical lesions derived from the literature associated with CPSP (n = 23), visual or auditory hallucinations (n = 28), or aphasia (n = 12). This set of lesions was utilized in a prior paper[19] and chosen because all syndromes could be caused by small subcortical lesions.[19] We chose to utilize this previously published lesion dataset to avoid any possible selection bias that could come from selecting cases specifically for the current study. As detailed in the initial report,[19] cases of CPSP were derived from a systematic search of pubmed.org with search terms of "central pain" or "central post-stroke pain". Inclusion criteria included patients who developed a pain syndrome in response to a focal intraparenchymal lesion of the brainstem or diencephalon as demonstrated by imaging. All hallucination lesions were also in the brainstem/diencephalon, although aphasia lesions could fall outside these structures. To ensure that differences in the geographic distribution of the aphasia lesions did not influence our results, we repeated our analysis excluding the aphasia lesions. Each lesion was traced by hand from published images onto a standardized brain atlas as described previously.[19] The original study using this dataset focused on connections common to lesions causing each symptom using a connectome derived from 98 healthy adults. A voxelwise statistical analysis focused on connections specific to pain (ie, 23 pain lesions vs 40 control lesions) was not performed. As in the original study,[19] no left/right flip was performed, which is not necessary for lesion network mapping analyses and has minimal impact on results (Fig S2).

Dataset 2: Thalamic Lesions

The second dataset included 43 patients with thalamic lesions from hemorrhagic stroke. Twenty of these 43 had CPSP, defined as spontaneous pain within a body area corresponding to the thalamic lesion that emerged at or after stroke onset.[10] These cohorts were intentionally matched, with no between-group differences in demographics, stroke severity, sensorimotor impairment, depression, cognitive function, lesion size, or lesion side.[10] All patients underwent 18F-FDG-PET–computed tomography (CT) approximately 2 months postlesion. All CPSP patients had pain at the time of PET scan, whereas controls did not. The original study using this dataset focused on metabolic differences between groups; no lesion location or connectivity analyses were performed.

For the current study, we returned to the original CT data for each patient. First, lesion locations were manually traced on each patient's CT scan using FSLeyes (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes). As in the original study,[10] left-sided lesion locations were flipped to the right hemisphere, which is not necessary for lesion network mapping (Fig S2) but is useful for maximizing statistical power in traditional analyses of lesion location or metabolic changes. Next, lesions were normalized to Montreal Neurological Institute (MNI) space using the SPM12 (Wellcome Trust Centre for Neuroimaging, University College London,

London, United Kingdom [http://www.fil.ion.ucl.ac.uk/spm] Clinical Toolbox [https://www.nitrc.org/projects/clinicaltbx]).[20] To ensure that our lesion tracings were accurate, we tested whether our lesion locations aligned with prior work on thalamic lesion locations associated with CPSP.[3–5] First, lesion subtraction analysis was conducted to identify voxels more frequently damaged in CPSP versus control lesions. Second, a voxelwise Liebermeister test was conducted to identify voxels statistically associated with CPSP using NiiStat (https://github.com/neurolabusc/NiiStat). The Liebermeister test examines differences in binomial data (eg, lesioned vs not lesioned voxels) and offers better sensitivity than the chi-squared test or the Fisher exact test in lesion mapping analysis.[21] This analysis used 2,000 permutations and focused on voxels occurring in at least 10% of lesions within a right thalamic mask from the Harvard Oxford Atlas distributed with FMRIB Software Library (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases, threshold of 50). Familywise error (FWE) correction was set at $p < 0.025$ for a 1-tailed test (equivalent to $p < 0.05$ for a 2-tailed test).

18F-FDG PET scans were acquired 30 minutes after intravenous injection of FDG as described in detail previously.[10] PET data from patients with left-sided lesions were flipped from left to right to maintain consistency with prior work.[10] Global mean normalization was performed by dividing each voxel value by the mean of all intracerebral voxels. The mean value was extracted by a whole-brain mask excluding extracerebral and ventricular voxels. There was no significant difference in global mean value between CPSP and the control group. PET images were spatially normalized to the MNI standard PET template and smoothed with an isotropic Gaussian kernel with an $8mm^3$ full width half maximum using SPM12. Although the original study used a $12mm^3$ kernel, we used a smaller smoothing kernel in our study to increase sensitivity for smaller brain regions.

Voxelwise Analyses of Lesion Connectivity (Datasets 1 and 2)

The network of brain regions functionally connected to each lesion location was identified using lesion network mapping as described previously (Fig 1).[14–17,22] Briefly, each lesion mask was used as a "seed region." Resting-state functional connectivity between each seed region and all other brain voxels was computed using a publicly available normative connectome dataset of 1,000 healthy controls.[23] Note that this 1,000-subject connectome is an updated and improved version of the 98-subject connectome used in prior work.[19] Processing of these scans has been fully described elsewhere,[23] including correction for motion and nonspecific variance using global signal regression. Resulting r maps were converted to a normal distribution using Fisher r-to-z transform and averaged across the 1,000 subjects.[14–17,22] This process yielded a single lesion network for each lesion location.

To identify significant differences in lesion connectivity between CPSP and control lesions, we started with lesion networks derived from Dataset 1 (23 CPSP vs 40 control lesions). Unthresholded lesion network maps were compared using a voxelwise 2-sample t test as implemented in Permutation Analysis of Linear Models (PALM) software (http://www.fmrib.ox.ac.uk/fsl/fslwiki/PALM). Two thousand permutations were applied, and an FWE corrected 2-tailed $p < 0.05$ using threshold-free cluster enhancement (TFCE) was considered statistically significant.

To test whether the connections identified in Dataset 1 were also significantly associated with CPSP in Dataset 2, we repeated the above univariate analysis using PALM software contrasting the lesion networks from Dataset 2 (20 CPSP vs 23 control lesions) within a voxelwise mask of significant results from Dataset 1 (CPSP > control). We used the same statistical parameters listed above, including 2,000 permutations and an FWE corrected $p < 0.05$ with TFCE. We repeated the analyses with the lesions in original orientation to check the laterality of connectivity differences according to the lesion side.

Because the above analysis could depend on choice of statistical threshold, we performed a second analysis of reproducibility comparing the unthresholded/uncorrected group difference maps from Dataset 1 and Dataset 2. The similarity between the two maps was computed via spatial correlation. Permutation testing with 10,000 permutations using randomly shuffled data (ie, mixing up which lesions were CPSP vs control lesions) was used to determine whether this spatial similarity was greater than expected by chance, the same method employed in prior work.[24]

To determine whether this lesion-based pain network topography was novel, or simply redundant with existing knowledge of pain network topography, we compared our lesion-based results to a pain network derived from the neuroimaging literature. Specifically, we generated a meta-analytic map of functional activations related to the term "pain" (516 studies) from Neurosynth (https://www.neurosynth.org/; Fig S4C).[25] We then compared the topography of this unthresholded Neurosynth map to the topography of our unthresholded lesion-based pain networks, both for Dataset 1 and for Dataset 2, using spatial correlation and the permutation method detailed above.

Voxelwise Analyses of Glucose Metabolism (Dataset 2)

For Dataset 2, we performed a voxelwise search for significant differences in glucose metabolism between CPSP and control lesions using a 2-sample t test with PALM software. Two thousand permutations were applied, and an FWE-corrected $p < 0.05$ using TFCE was considered statistically significant. Note that this statistical approach differs from prior work on this dataset,[10] which used an uncorrected threshold and less rigorous methods for identifying significant clusters.

Relationship between Lesion Connectivity and Glucose Metabolism

Voxelwise differences in connectivity from Dataset 1, voxelwise differences in connectivity from Dataset 2, and voxelwise differences in glucose metabolism from Dataset 2 were thresholded ($p_{\text{TFCE FWE-corrected}} < 0.05$), binarized, and overlaid. This conjunction analysis identified voxels that were significant across all 3 analyses, which we will refer to as our "pain network." Voxels surviving this analysis fell within two distinct clusters: (1) a cluster encompassing ipsilesional M1 and primary somatosensory

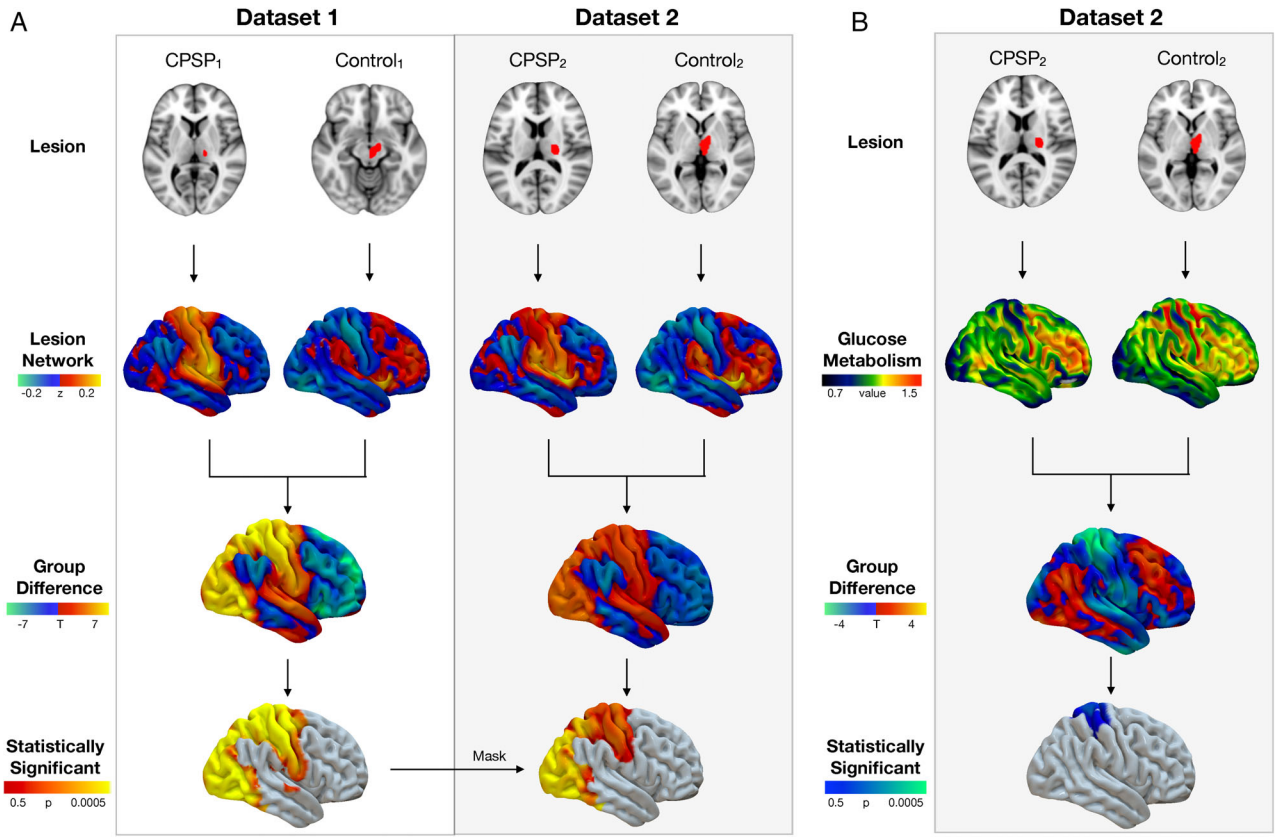

FIGURE 1: Methods for identifying brain networks for pain based on focal brain lesions. (A) Two independent datasets of lesion locations (red) associated with central poststroke pain (CPSP) or not associated with CPSP (control) were analyzed (Row 1). Functional connectivity between each lesion location and the rest of the brain was computed using a publicly available connectome dataset of 1,000 healthy controls (Row 2). Connections specific to CPSP versus control lesions were identified (Row 3), and statistical significance was assessed through permutation ($p_{TFCE\ FWE\text{-}corrected} < 0.05$, Row 4). Positive correlations with CPSP lesions are shown in hot colors, and negative correlations (anticorrelations) are shown in cool colors. (B) In Dataset 2, each lesion patient (Row 1) underwent metabolic positron emission tomography imaging approximately 2 months after their stroke (Row 2). Differences in glucose metabolism between CPSP and controls were identified (Row 3), and statistical significance was assessed using permutation ($p_{TFCE\ FWE\text{-}corrected} < 0.05$, Row 4). Hypermetabolism in the CPSP group is shown in hot colors, and hypometabolism is shown in cool colors. FWE = familywise error; TFCE = threshold-free cluster enhancement.

cortex (S1) and (2) a cluster encompassing contralesional occipital cortex. These clusters were used as regions of interest (ROIs) for subsequent analyses.

To test whether lesion connectivity was correlated with postlesion metabolism, we computed functional connectivity between each lesion location in Dataset 2 and each ROI using a standard seed-to-seed approach. Specifically, the time course of the average blood oxygen level-dependent signal within each lesion location and each ROI was extracted from each individual in the normative connectome. A Pearson correlation coefficient was computed, and resulting R values were converted to a normal distribution via Fisher r-to-z transform. Values were averaged across the 1,000 subjects, generating a single value reflecting the functional connectivity of each lesion location to each ROI. Mean glucose metabolism within each ROI was computed for each patient in Dataset 2 by averaging the voxel intensities in the preprocessed 18F-FDG-PET images using the fslstats tool included with FMRIB Software Library v6.0 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils). For each ROI, the correlation between connectivity and metabolism across individual subjects was assessed using Pearson correlation coefficient.

Relevance for CPSP Neuromodulation Targets

We performed 3 independent analyses to test whether our pain network, derived from lesion connectivity and postlesion metabolism, might be relevant for neuromodulation treatments such as brain stimulation, as follows.

Relation to Prior Neuromodulation Targets for Pain from the Literature

To generate an unbiased list of neuromodulation targets previously used to treat CPSP, we relied on a recent comprehensive review.[9] Neuroanatomical targets were included regardless of efficacy, but thalamus was excluded, as network connectivity to this target would be confounded by the lesion locations themselves. This process resulted in 12 neuromodulation targets previously used for pain (Table S1). Each target was converted into an a

priori ROI using MNI coordinates from prior publications. Stimulation coordinates were used whenever possible, as was the case for dorsal lateral prefrontal,[26] anterior cingulate cortex,[27] secondary somatosensory cortex,[28] and posterior parietal cortex.[29] Average coordinates from hand movement task functional magnetic resonance imaging (fMRI) studies were used for M1 and S1.[30] Coordinates for the premotor cortex and supplementary motor area were defined by relative distance to M1.[31] Finally, coordinates from a prior neuroimaging meta-analysis were used for the periaqueductal gray.[32] ROIs were defined by a 3mm-radius sphere centered on each MNI coordinate.

Functional connectivity between each lesion location and each ROI was computed as described above, both for Dataset 1 and for Dataset 2. Mean glucose metabolism of each ROI was also computed as described above. A 2-way analysis of variance (ANOVA) was used to test for an interaction between CPSP symptoms and ROI connectivity or metabolism. To determine which ROIs drove any significant results identified in the ANOVA, post hoc 2-sample t tests were performed wherein $p < 0.05$ was considered statistically significant. ROIs that showed the most significant differences between CPSP and control lesions across all 3 analyses were identified.

As a comparison, neuromodulation target ROIs were also overlayed on our unthresholded Neurosynth pain map (detailed above). Overlap between each ROI and the meta-analytic map was quantified by averaging the z values of each voxel in the activation map that fell within each ROI mask.

Relation to Individualized TMS Sites Targeting M1

Second, we retrospectively assessed whether individualized TMS sites intersecting our pain network were associated with better pain response. We utilized the data from a double-blind, randomized, sham-controlled, crossover trial investigating the effect of high-frequency repetitive TMS (rTMS) targeting M1 on chronic neuropathic pain.[33] In each patient, rTMS was delivered to the brain location that best evoked a muscle twitch in the hand (motor hotspot), resulting in some variation in the stimulation site across subjects. This stimulation site was recorded in each patient using neuronavigation, coregistered to each patient's MRI, then transformed into common atlas space (MNI152).[33] This set of coordinates was shared with us by the original authors (n = 34), along with whether each patient was a "responder" or "nonresponder," the primary outcome measure from this trial.[33] "Response" was defined using a combination of pain scores, quality of life scores, and analgesic drug intake.[33] We maintained this definition for our own analysis to stay consistent with the original publication and primary outcome measure from this trial.

For each individualized stimulation coordinate (Supplementary Table S2), we modeled the electrical field induced by a figure-of-eight TMS coil using SimNIBS 3.1.2 (https://simnibs.github.io/simnibs/build/html/index.html). The electric field intensity was normalized with respect to the maxima to allow for comparability across subjects. For each patient, we computed the mean electric field strength within the sensorimotor cluster of our pain network. Patients were binned into 2 groups based on whether their stimulation to our pain network was above average or below average. We then tested for a difference in responder rates between groups using Fisher exact test. For comparison purposes, we repeated this analysis using an a priori ROI in M1[30] rather than the sensorimotor ROI from our pain network.

Prospective Targeting of Our Pain Network Using TMS

Third, we prospectively tested whether TMS directly targeting our pain network was capable of improving pain in patients with CPSP. Patients were recruited from the Department of rehabilitation medicine at Yongin Severance Hospital, Yongin-si, Gyeonggi-do, Republic of Korea. All patients were medication-refractory and had pain rated moderate to severe in intensity (≥4/10 on a numeric rating scale). Patients had to provide signed informed consent to participate. The hand motor hotspot was identified in each patient, and motor threshold was measured using standard procedures.[34] The location of the motor hotspot was recorded using an MRI-guided neuronavigation system (Brainsight; Rogue Research, Montreal, Quebec, Canada). The TMS target in our pain network was identified by taking the MNI coordinates of our sensorimotor cluster (19, −36, 67) and transforming these coordinates to the patient's MRI using SimNIBS 3.1.2. To explore whether the treatment site in our pain network differed from the traditional treatment site over the hand motor hotspot, we modeled the electric field generated by the TMS coil at both sites using SimNIBS 3.1.2 and patient-specific MRI scans. For each simulation, electric field strength was normalized to its maximum. For each patient, stereotactic coordinates of the coil location was projected on the brain surface,[33] and a 3mm-radius sphere centered on each MNI coordinate of motor hotspot was created. Our sensorimotor cluster was transformed to the patient's MRI using FLIRT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT). We computed the ratio of the mean E-field strength within our sensorimotor cluster to the mean E-field strength within the hand motor hotspot under two conditions: when directly targeting our sensorimotor cluster and when targeting the hand motor hotspot. The ratio of the mean electric field strength between the conditions were compared using Mann–Whitney U test.

rTMS was delivered with a Magstim (Whitland, UK) stimulator through a figure-of-eight coil (Double 70mm Air Film Coil). Neuronavigation was used in all sessions, targeting the coordinates for our pain network on the patient's MRI. Stimulation parameters were based on previous work on chronic pain.[33] One session of stimulation consisted of 20 consecutive trains of 80 pulses delivered at 20Hz, at 80% of motor threshold and separated by an intertrain interval of 84 seconds (ie, a total of 1,600 pulses over a 27-minute session). Ten sessions were performed, five times per week for 2 weeks, and pain intensity was assessed before the first and after the last session. Before and after all rTMS sessions, the patients were asked whether they had experienced any adverse effects such as headache or worsened symptoms. A "response" to TMS was defined as ≥30% pain relief, a commonly used outcome metric that relates to a clinically meaningful change in pain.[35,36] To ensure that our results were not dependent on this cutoff, we repeated our analysis using ≥40% pain relief, an alternative cutoff used in a recent open-label rTMS study targeting M1 in CPSP.[37] Note that this simple

definition of TMS response differs from the complex definition used in our retrospective TMS dataset.[33]

Study Approval

Data collection in the thalamic pain/PET cohort (Dataset 2) and the prospective TMS trial in 3 patients were both approved by the ethics committee at Yongin Severance Hospital, Yongin-si, Gyeonggi-do, Republic of Korea. Data analysis (all datasets) was approved by the ethics committee at Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, both in Boston, Massachusetts, USA.

Results

Lesion Location

We analyzed two independent lesion datasets, both of which have been published previously.[10,19] Lesion locations associated with pain and control lesions not associated with pain were mapped to a common brain atlas for both Dataset 1 (n = 63 literature lesions, 23 of which were associated with CPSP) and Dataset 2 (n = 43 thalamic lesions, 20 of which were associated with CPSP; see Fig 1A). To ensure that this lesion mapping was accurate and consistent with the literature, we performed a voxel lesion–symptom mapping analysis using the 3-dimensional (3D) lesions from Dataset 2. Consistent with prior work,[3–5] thalamic lesions associated with CPSP were more likely to occur in VPL or near the boundary between VPL and anterior pulvinar nucleus (FWE corrected $p < 0.05$, Fig S1).

Lesion Network Mapping

Next, we identified the network of brain regions functionally connected to each lesion location and identified connections significantly associated with CPSP (see Fig 1A). Similar to prior work,[14–17,22] we computed functional connectivity between each lesion location and the rest of the brain using resting-state fMRI data from a large normative cohort (n = 1,000).[23] Relative to control lesions, CPSP lesions showed stronger connectivity to bilateral M1, S1, and occipital cortex ($p_{TFCE\ FWE\text{-}corrected} < 0.05$; Fig 2, Table S3). The connectivity pattern identified in Dataset 1 (see Fig 2A) was validated in Dataset 2 (see Fig 2B), and highly consistent across the two independent datasets (spatial $r = 0.82$, $p < 0.0001$). These results were independent of whether lesion locations were analyzed in their original position or flipped to a single hemisphere (Fig S2) and whether aphasia lesions were included in the control group (Dataset 1, Fig S3). This lesion-based

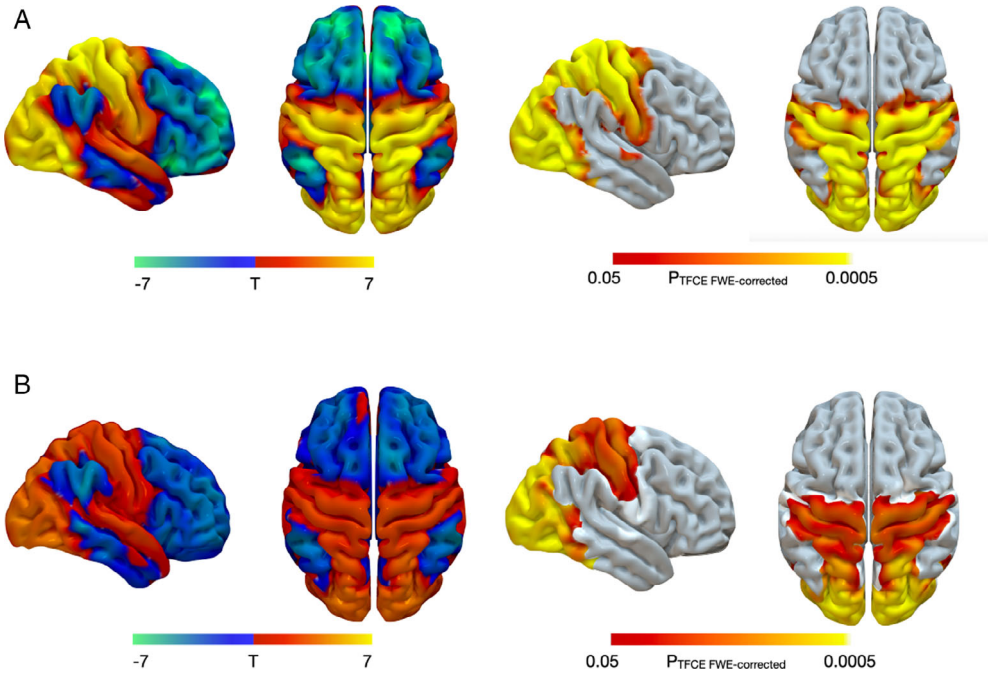

FIGURE 2: Connections specific to pain lesions are consistent across two independent datasets. Differences in connectivity between lesion locations associated with central poststroke pain (CPSP) and control lesions were similar in Dataset 1 (A) and Dataset 2 (B). The left column shows unthresholded maps, which showed similar topography across the two datasets (spatial $r = 0.82$, $p < 0.0001$, 10,000 permutations). The right column shows voxels significantly more connected to pain than control lesions after voxelwise correction for multiple comparisons ($p_{TFCE\ FWE\text{-}corrected} < 0.05$). Significant voxels in Dataset 1 (A, second column) were identified using a whole-brain search, whereas significant voxels in Dataset 2 (B, second column) were identified using the results of Dataset 1 as an a priori search space (white underlay). Positive correlations with CPSP lesions (relative to control lesions) are shown in hot colors, and negative correlations (anticorrelations) are shown in cool colors. FWE = familywise error; TFCE = threshold-free cluster enhancement.

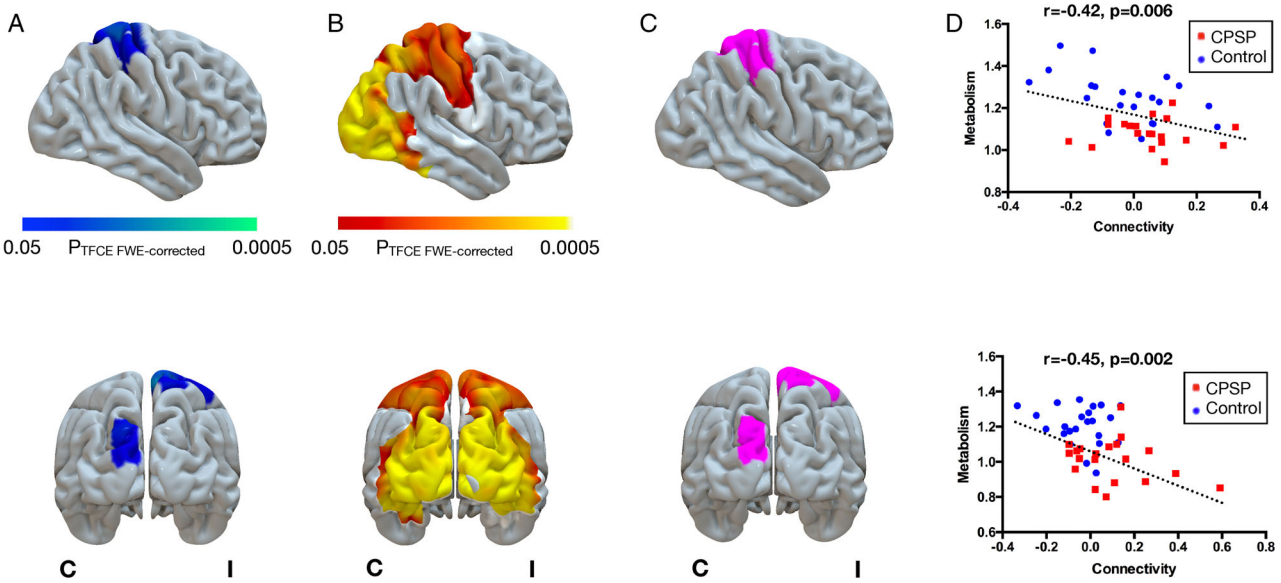

FIGURE 3: Differences in metabolism after stroke are related to differences in lesion connectivity. (A, B) Brain regions exhibiting significant decreases in glucose metabolism poststroke (A) overlapped the brain regions showing significant differences in lesion connectivity (B). (C) A conjunction analysis identified voxels that were significant in both the metabolism and connectivity analyses, with one cluster in the ipsilesional sensorimotor cortex and another in the contralesional occipital cortex. (D) Connectivity from each lesion location (n = 43) to the ipsilesional sensorimotor cortex (upper row) and the contralesional occipital cortex (bottom row) was significantly correlated with postlesion metabolism. C = contralesional; CPSP = central poststroke pain; FWE = familywise error; I = ipsilesional; TFCE = threshold-free cluster enhancement.

topography for pain was different than existing knowledge of pain topography from the neuroimaging literature, as the above lesion networks were different from the Neurosynth map for pain (Dataset 1: spatial $r = 0.09$, $p = 0.28$; Dataset 2: spatial $r = 0.05$, $p = 0.37$; Fig S4).

Lesion Connectivity and Glucose Metabolism

To test whether differences in lesion connectivity were related to remote changes in metabolism, we analyzed 18F-FDG-PET obtained in the patients with thalamic lesions (Dataset 2) obtained approximately 2 months after their stroke (see Fig 1B). Relative to controls, patients with CPSP exhibited decreased glucose metabolism in ipsilesional M1, ipsilesional S1, and contralesional occipital cortex ($p_{\text{TFCE FWE-corrected}} < 0.05$; Fig 3). These metabolic differences spatially overlapped the connectivity differences identified above. A conjunction analysis identified 2 regions that showed both significant differences in connectivity and significant differences in metabolism: (1) ipsilesional sensorimotor cortex and (2) contralesional occipital cortex. We will refer to the results of this conjunction analysis as our "pain network." Lesion connectivity to each region in our pain network was significantly correlated with postlesion metabolism, both for sensorimotor cortex (Pearson $r = -0.42$, $p = 0.006$) and occipital cortex ($r = -0.45$, $p = 0.002$). The more connected the lesion location was to these regions, the greater the amount of poststroke hypometabolism.

Therapeutic Relevance of the Pain Lesion Network

We identified 12 published brain stimulation targets for CPSP, of which ipsilesional M1 had the best evidence of therapeutic efficacy (Fig 4A).[12] These 12 targets intersected our lesion-based pain network to varying degrees. A 2-way ANOVA revealed a significant pain × ROI interaction for Dataset 1 connectivity ($F_{11,\ 732} = 12.88$, $p < 0.0001$), Dataset 2 connectivity ($F_{11,\ 492} = 2.067$, $p < 0.05$), and Dataset 2 glucose metabolism ($F_{11,\ 492} = 2.045$, $p < 0.05$). Post hoc 2-sample t tests revealed that ipsilesional M1 was the only target to show significant differences between pain and control lesions across all 3 analyses: (1) Dataset 1 connectivity ($p < 0.5 \times 10^{-6}$), (2) Dataset 2 connectivity ($p < 0.05$), and (3) Dataset 2 glucose metabolism ($p < 0.005$; Fig S5, Table S4). In other words, ipsilesional M1 aligned with our lesion-based pain network significantly better than other neuromodulation targets with less evidence of efficacy.

To test whether a pain network based primarily on neuroimaging correlates of pain (rather than lesions) would also highlight this therapeutic target, we examined the intersection of our 12 neuromodulation targets with a map of "pain" from Neurosynth (Table SS1, Fig S6). Whereas several prior neuromodulation targets intersected this map, the therapeutic target with the best evidence of efficacy (ipsilesional M1) did not.

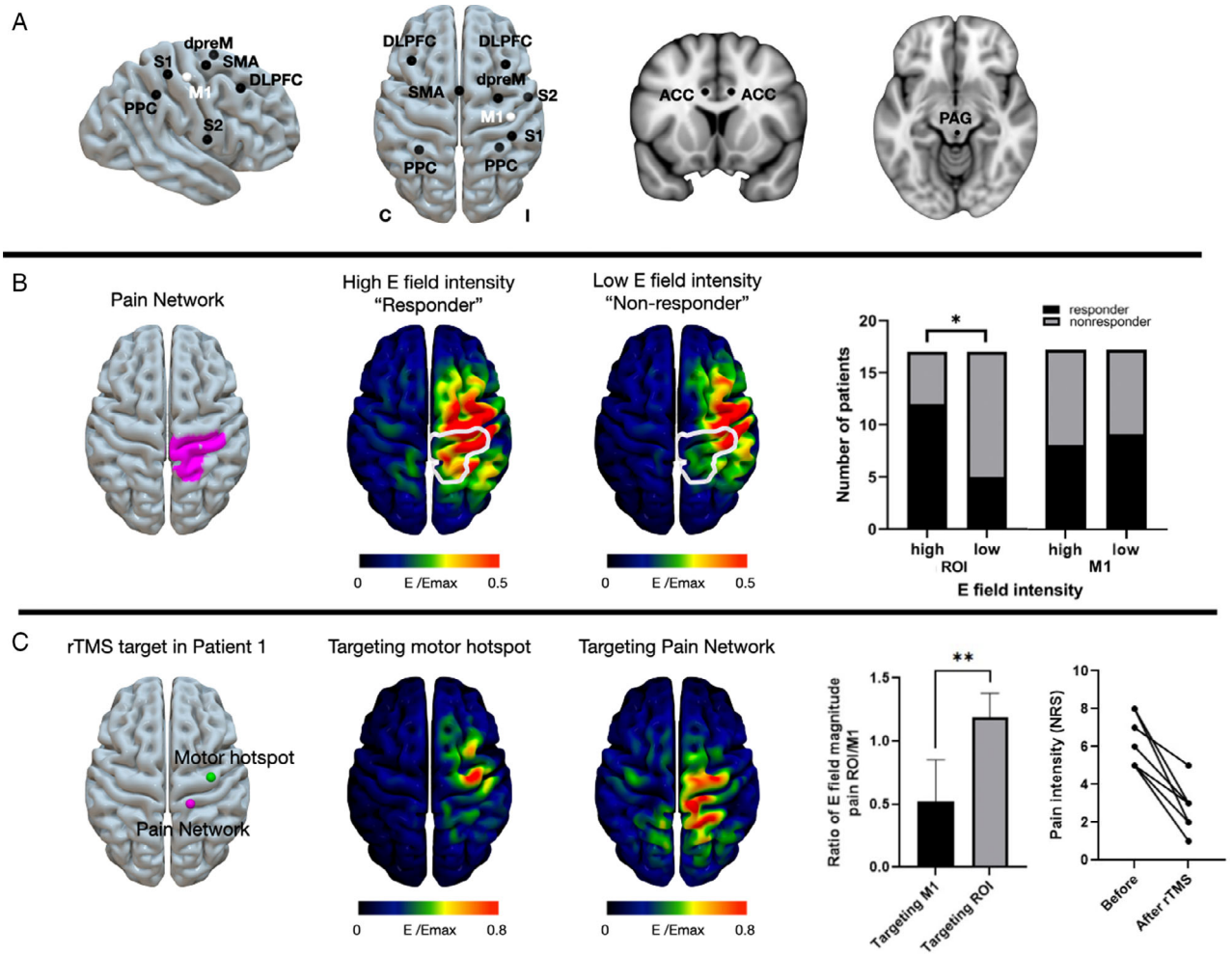

FIGURE 4: Potential therapeutic relevance of our lesion-based pain network. (A) Among 12 brain stimulation targets that have been used for pain, primary motor cortex (M1, white) aligns best with our lesion-based pain network and is supported by the best evidence of efficacy. (B) Among 34 patients who received repetitive transcranial magnetic stimulation (rTMS) to the hand motor hotspot for pain, patients who had higher electric field intensity within our pain network (pink region, white outlines) were more likely to respond (right, *$p < 0.05$). Examples of patients with "high" versus "low" simulated electric field intensity within our pain network are shown (middle). In contrast, the intensity of simulated electric field within M1 was not related to efficacy of rTMS (right). (C) Among 7 patients who received open-label rTMS directly targeting our pain network, 6 patients were responders. Our rTMS target for pain (pink dot) was different than the traditional target over the hand motor hotspot (green dot), resulting in very different electric fields (middle, **$p < 0.005$). Six of 7 patients showed significant (≥30%) pain relief without adverse effects (right). ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; dpreM = dorsal premotor cortex; NRS = numeric rating scale; PAG = periaqueductal gray; PPC = posterior parietal cortex; ROI = region of interest; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SMA = supplementary motor area.

Second, we retrospectively assessed the relationship between the electrical field strength within our pain network and the analgesic effects of rTMS (see Fig 4B). Although all patients received rTMS targeting M1, patients whose stimulation site better intersected our pain network were more like to respond ($p < 0.05$). In contrast, TMS electric field strength within M1 itself was not associated with response ($p = 0.73$).

Finally, we prospectively targeted our pain network with rTMS in 7 patients with central poststroke pain (see Fig 4C, Table S5). TMS targeting the sensorimotor cluster of our pain network generated a very different electric field than TMS targeting M1 ($p < 0.005$; see Fig 4C). No patient experienced any severe adverse effects during or after the rTMS. Six of 7 patients (85.7%) showed significant pain relief, independent of whether relief was defined as ≥30%[35,36] or ≥ 40%[37] improvement in pain scores.

Discussion

There are 3 novel findings. First, lesions causing pain are associated with a specific pattern of functional connectivity to remote brain regions that is consistent

across independent lesion datasets. Second, these functional connectivity differences are correlated with changes in poststroke glucose metabolism. Finally, our lesion-derived pain network aligns with retrospective and prospective data on pain improvement following neuromodulation, suggesting potential therapeutic relevance.

A Lesion-Based Network for Pain

There have been extensive efforts to define the neuroanatomy of pain using a variety of neuroimaging techniques.[38] Here, we take a complementary approach, deriving a network for pain based on brain lesions causing pain. Our results add to the existing literature, as the topography of our lesion-based pain network (although highly consistent between independent lesion datasets) was substantially different from a Neurosynth map of pain derived from the existing neuroimaging literature. Similarly, our lesion-based network for pain aligned better with the therapeutic efficacy of different neuromodulation targets for pain than this Neurosynth map. These results are consistent with an expanding literature suggesting that there is unique value for causal mapping of lesion-based symptoms compared to studying functional neuroimaging correlates of those symptoms.[39]

Our finding that lesions associated with CPSP are characterized by a specific pattern of brain connectivity is consistent with a growing literature on lesion network mapping across many different neuropsychiatric symptoms.[13–17,19] These studies show that lesions causing the same symptom can occur at different neuroanatomical locations but map to a common functionally connected brain network. By comparing lesions causing pain to control lesions not causing pain, we identified a network specific to pain lesions.

Our paper is not the first to use lesion network mapping to study CPSP.[2,19] However, our study is the first to test for consistency across independent datasets of pain lesions, to relate connectivity to metabolism, or to relate connectivity to TMS efficacy. Furthermore, our study differs from prior lesion network mapping studies of pain by focusing on connections *specific* to pain lesions. Both Boes et al and Elias et al focused primarily on connections *common* to lesions causing pain. Both studies highlighted the insula as a key region connected to most if not all lesions causing CPSP.[2,19] However, connectivity to the posterior insula is not specific to CPSP lesions. This does not imply that the insula is unimportant in pain perception, but rather that connectivity to the insula is not specific to CPSP. Given the role of the insula in a variety of functions that go well beyond interoception or pain perception,[40] this lack of specificity is perhaps not surprising. Our results show that the most specific connections for CPSP were to the sensorimotor cortex and a region in the occipital cortex. These results differ from the most specific connections reported in Elias et al; however, we have greater confidence in the current results because our connectivity pattern was (1) generated using better matched control lesions, (2) validated across independent lesion datasets, (3) associated with changes in poststroke metabolism, and (4) aligned with retrospective and prospective data on neuromodulation targets for pain.

Relating Connectivity to Metabolism

An important finding in the current paper is the correlation between differences in lesion connectivity and postlesion metabolism. Lesion network mapping studies identify remote brain regions that are functionally connected to the brain region damaged by the lesion.[13–17,19,41] An assumption in these studies is that the lesion has a functional effect on this connected brain region. This concept of diaschisis is not new,[42] but direct support for this hypothesis in humans has been limited. Anatomical connectivity with lesion locations has been linked to brain atrophy,[43] and lesions to a cerebral hemisphere have been related to hypometabolism in the contralesional cerebellum.[44] However, to our knowledge, the current study is the first to link individual differences in metabolism in a remote brain region to individual differences in connectivity between the remote brain region and the lesion location.

As expected, we observed a negative correlation between functional connectivity and postlesion metabolism (see Fig 3). Positive functional connectivity was associated with postlesion hypometabolism, whereas negative functional connectivity (ie, anticorrelation) was associated with postlesion hypermetabolism. Given the increased popularity of lesion network mapping in our group[13–17,19,41] and others,[2] the current study provides important validation that differences in lesion connectivity are associated with differences in functional activity, consistent with the diaschisis model.[42]

Although lesion connectivity and metabolism were correlated, it is worth noting that these sources of information were not identical. Many regions showed significant differences in connectivity but did not show significant differences in metabolism (eg, contralesional sensorimotor cortex or ipsilesional occipital cortex). This discrepancy may reflect the tendency of functional connectivity to identify bilateral networks or sensitivity to polysynaptic connections. Combining lesion network mapping with metabolic imaging in poststroke patients may allow for more specific or precise identification of therapeutic targets. Similarly, lesion network mapping might be used to highlight a priori regions for further investigation with poststroke imaging modalities.

Finally, metabolic abnormalities may help guide the type of neuromodulation needed to "normalize" aberrant

brain networks affected by focal lesions.[42] For example, high-frequency M1 stimulation is more effective at diminishing pain than low-frequency stimulation.[12] This finding is consistent with M1 hypometabolism in patients with pain and increases in metabolism following high-frequency M1 TMS.[45]

Relevance for Neuromodulation

We found a clear link between lesion locations causing pain and M1, the neuromodulation target with the best evidence of efficacy for improving pain.[9,11,12] Our voxelwise analyses specifically implicate the anterior wall of the central sulcus, the part of the precentral gyrus where M1 resides.[46] At first glance, this may seem to be a trivial result, as M1 is already known to be an effective TMS target for pain. However, this M1 target was identified largely through trial and error, and many other brain regions have been targeted and found not to be as effective (see Fig 4C). Because our lesion-based approach differentiates M1 from these other targets, our lesion-based pain network may help identify therapeutic targets for neuromodulation that complement traditional functional neuroimaging.

It is important to note that although our lesion-based pain network includes M1, it also extends beyond M1, which may have implications for improving neuromodulation treatments for pain. Specifically, our M1 region extended into S1 and the superior parietal lobe. These regions have been implicated in sensation or attentional modulation of sensory perception,[47] and rTMS targeting the "motor hotspot" stimulates S1 in addition to M1.[48] Whether stimulation directly targeting S1 (rather than M1) can improve pain is unclear, with mixed results.[11,49,50] Given that noxious stimuli undergo parallel processing in S1 and M1,[51] it is possible that neuromodulation treatments targeting S1 and M1 simultaneously (ie, the sensorimotor cluster in our pain network) could yield more benefit than M1 or S1 alone. Our retrospective analysis of data from a recent rTMS randomized clinical trial supports this hypothesis, as the electric field strength in our pain network, but not M1, was associated with treatment response. Moreover, our prospective open-label pilot study suggests that high-frequency rTMS targeting the sensorimotor cluster of our pain network may have therapeutic value.

To our knowledge, this is the first paper to derive a brain network based on lesions causing a symptom, refine a therapeutic target for that symptom, and then prospectively stimulate that target and show symptom improvement. This provides proof-of-concept and demonstrates feasibility for this methodological approach, with an open-label response rate (6/7 patients, 85.7%) that is comparable to or better than other open-label response rates in the literature (61%[37]). However, results in this small number of patients should not be overinterpreted. Future randomized controlled studies in larger numbers of patients are needed to determine whether rTMS targeting the sensorimotor cluster of our pain network is better than placebo or traditional rTMS targeting M1.

Beyond the sensorimotor cortex, our voxelwise analyses also identified extrastriate visual cortex (V3/V3A). This finding was unexpected, as this region has not previously been implicated in CPSP. However, this region has been implicated in other pain conditions such as fibromyalgia and migraine headaches.[52,53] TMS to this region may prevent or abort migraine pain,[54] and training with visual feedback (which presumably modulates this visual brain region) may improve phantom limb pain.[55] As such, it is possible that our lesion-based network for poststroke pain may not be specific to CPSP, but relevant to pain more generally. Such a hypothesis is consistent with other recent lesion network mapping findings. For example, our lesion-based network for depression is relevant to depression more generally, including therapeutic targets for brain stimulation.[17,56] Whether the current lesion-based network for pain generalizes to other pain conditions is an important topic for future work.

Limitations

There are several limitations. First, lesion tracing based on published images (Dataset 1) or CT scans (Dataset 2) is an imperfect process. Nevertheless, prior work suggests that 2D approximation of a 3D lesion is sufficient for lesion network mapping,[19] and our results are consistent with previous CPSP studies that traced lesions using high-resolution MRI.[3–5] Furthermore, any lesion tracing errors should bias against the current findings, namely, significant between-group differences in lesion connectivity that are consistent across independent datasets. Second, our lesion datasets consisted of subcortical lesions, but cortical lesions (eg, parietal cortex) have also been reported to cause pain.[8] For example, Schmahmann and Leifer[8] reported 6 patients who developed hemibody pain following lesions in the parietal cortex. Five of the 6 lesions appear to overlap our network or the white matter just inferior to our network; however, dedicated analyses including more cortical lesions (and control lesions not causing pain) are needed before any clear conclusions can be drawn. Third, we classified patients according to the symptoms that were present when the PET scan was performed (Dataset 2). It is possible that some of our controls developed pain at a later date; however, any such patients would bias us against the present findings. Fourth, the clinical significance of our lesion network and any improvement in neuromodulation targets based on this network remain to be tested in prospective randomized clinical trials. Fifth, our results address *where* to stimulate for pain, but not *how* or *when* to stimulate for pain. Even if the neuroanatomical target is correct, the parameter space for TMS is large and not fully understood. For example,

one study showed that 10Hz rTMS with 1,500 pulses induced analgesic effects, but 10 and 20Hz stimulation with 3,000 pulses had no effect.[57] The ideal parameters and protocols for improving CPSP require significant work and testing in randomized–controlled trials. Lastly, per convention in the pain literature,[35,36] we used a binary cutoff to classify patients as "responders" or "nonresponders." We showed our conclusions are independent of different literature-based cutoffs for pain improvement, but did not analyze percentage pain change as a continuous value, as the reliability of this measure is uncertain.[35,36]

Conclusions

Lesions causing CPSP are characterized by a specific pattern of brain connectivity. These connectivity differences are associated with metabolic differences in remote brain regions. Our lesion-based pain network aligns with the efficacy of neuromodulation targets for pain and provides testable hypotheses for potentially improving neuromodulation treatment for pain.

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Potential Conflicts of Interest

Nothing to report.

Author Contributions

N.Y.K., J.J.T., and M.D.F. contributed to the conception and design of the study; N.Y.K., J.J.T., Y.W.K., D.B., J.J., J.L., C.Q., and R.P. contributed to the acquisition and analysis of data; N.Y.K., J.J.T., and M.D.F. contributed to drafting the text or preparing the figures.

Data Availability

The data analyzed in this study are available in publications as well as from the corresponding author.

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